

**REMARKS**

Claims 1-13 and 23 were pending in the present application. By this Amendment, Applicants have amended claims 1, 5, 7, 8, 9, and 10 by incorporating subject matter from dependent claims therein. Support for the claim amendments can be found throughout the specification and claims as originally filed. Applicants have canceled claims 2-4, 6, 11, and 23, without prejudice to the right to present the canceled subject matter in a future continuing application. The present Amendment does not introduce any new matter and thus, its entry is respectfully requested. Upon entry of the present Amendment, claims 1, 5, 7-10, and 12-13, as amended, will remain pending and under examination.

**The July 31, 2006 Office Action**

**Previous Rejections Withdrawn**

The Examiner indicated that the rejections set forth in the previous Office Action under 35 U.S.C. §103(a) have been withdrawn in light of Applicants' June 9, 2006 Amendment.

In response, Applicants acknowledge and appreciate the withdrawal of these rejections.

**Examiner's new claim rejections under 35 U.S.C. §103(a)**

Claims 1-13 and 23 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over the previously cited Fromherz reference, in view of a newly cited publication by Plugge, et al., dated March 3, 2000. The Examiner again has acknowledged that the Fromherz reference fails to teach the use of a medium which has a salt concentration of less than or equal to 100mM/L, or the use of an array comprising a multiplicity of cells immobilized on different electrodes for the purpose of testing the effects of a multiplicity of substances on the target cell component.

In rejecting the claims, the Examiner therefore relies on the Plugge reference for its teaching

of a method that includes contacting the cell with amantadine, cesium and barium in a medium which has a total salt concentration of less than 100 mM/L (page 1642, column 3, page 1643, column 1, lines 11-21, and column 3, lines 45-55, and Fig. 4), measuring the signal at the electrode on which the cell is immobilized, and determining the effect of the substance (amantadine, cesium or barium) on the measurement signal. The Examiner has thus concluded that it would have been obvious to combine the method of Fromherz with the low salt concentration teachings of Plugge in a method to determine whether a substance modulates a target component of a cell, such as a potassium channel. The Examiner's rationale essentially is that the ordinarily skilled artisan would have been motivated to use the lower salt concentration, and would have had a reasonable expectation of success in doing so because the methods of Fromherz and Plugge are similarly drawn to the analysis of potassium channels in cells and to determining the effects of modulators on such potassium channels through electrochemical detection. The Examiner also has concluded that because (in the Examiner's view) it would have been obvious to test a single substance in such a method, the testing of multiple substances represents only a slight further modification of the method and thus also would have been obvious.

In response, without conceding the correctness of the Examiner's position, but to expedite allowance of the application, Applicants have amended the claims to better reflect the present invention. Applicants also present the following comments on the art cited by the Examiner.

Applicants note that Plugge et al. describe the expression of the viral protein Kcv in *Xenopus laevis* oocytes. The protein contains a sequence motif, which resembles a highly conserved domain of potassium channel proteins. In order to determine whether recombinantly expressed Kcv functions as an ion channel in oocytes, the voltage at the oocytes was measured by means of patch

clamps. The measurement was conducted in a solution having a total salt concentration  $\leq$  100 mmol/L.

However, the method described by Plugge et al. differs from the method according to the present invention in two significant aspects:

First, Plugge et al. only disclose measurements conducted for voltage-dependent ion channels. Plugge, however, does not give any hint as to ion-channel/receptor systems containing a ligand-controlled or mechanically controlled ion-channel, as reflected in the presently amended claims. It is well-known to the person skilled in the art that these different kinds of ion-channels each exhibit a completely different biological behavior and are therefore not comparable.

Moreover, Plugge et al. uses the patch clamp technique for voltage measuring. In particular, Plugge et al. describe the conduction of “*voltage clamp assays*” (page 1642, middle column, second paragraph). This invasive method leads to the generation of a fixed linkage between the cell membrane and the measurement device and is known to be used for intracellular voltage measuring.

According to the present invention, the cells are immobilized on extracellular potential sensitive electrodes (see, for example, claim 1(a)). Such arrangement leads to a gap between the electrode and the cell.

Based on these different constructions of the measurement devices, the reduction of the salt concentration in voltage measurement for voltage-dependently controlled ion channels according to Plugge et al. aim at an amendment of the biological reversal potential at the cell membrane.

However, a reduction of the salt concentration at the voltage-controlled or mechanically controlled ion channels according to the present invention leads to an increase in the resistance at the gap between electrode and cell and thus to an increase in signaling. The signal increase in turn leads

to a significant improvement of the signal-to-noise ratio.

The prior art and especially Plugge et al. do not provide any hint to this circumstance. Thus, the skilled person had no reason to use the conditions necessary for conducting the intracellular patch clamp technique according to Plugge et al. in an extracellular measurement technique as described in Fromherz et al. Thus, the claims as presently amended are not rendered obvious by the prior art. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Applicants believe that the claim amendments presented herein, and the remarks presented above, fully address the Examiner's concerns as set forth in the July 31, 2006 Office Action and that the claims are in condition for allowance. Reconsideration of the instant application and an early notice of allowance are therefore requested. The Examiner is invited to telephone the undersigned if it will expedite allowance of the application.

Application No. 10/666,530  
Reply to Office Action of July 31, 2006  
Amendment dated October 31, 2006

No fee is believed due in connection with the filing of this Amendment. If, however, any fee is required, authorization is hereby given to charge such fee, or credit any overpayment, to Deposit Account No. 02-2135.

Respectfully submitted,

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